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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,644	07/13/2001	Daniel Vanna Siev	018813/027 2492	2686

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	9

DATE MAILED: 05/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/905,644	SIEV ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communicati n appears on th c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *11,12,16,30-32,39,40,47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-15,17-29,33-38,41-46 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group II, namely pyridone, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that it would not be serious search burden to search elected pyridone with non-elected pyrazinone as they 'are sufficiently related so as to be properly examinable together'. Upon further consideration, examiner noted an error in the number of claims included in each of the two groups. Hence the following revised restriction is made.

Claims 1-49 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8,11-12, 16, 30-36, 39-44 and 47-48, drawn to compound of formula I where Q= N, composition and method of use, classified in class 544, subclasses 337, 408, class 514 subclass 252.10 and other classes and subclasses depending upon the choice of R group.

II. Claims 1-10,13-15, 17-29, 33-38, 41-46 and 49, drawn to compound of formula I where Q= CR_4, composition and method of use, classified in class 546, subclass 297, class 514, subclass 345 other classes and subclasses depending upon the choice of R group.

The inventions are distinct, each from the other because of the following reasons:

Invention I and II are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core namely pyrazinone versus pyridinone Consequently, the groups have different classifications and require

separate prior art searches. They can be made and used independently. Art which may render obvious or anticipate one of the groups would not necessarily do the same for the other group. Each can support a patent, as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group. The large number of heterocyclic rings and heteroaryl ring permitted as substituents would involve extensive classification and search, hence the search would be a serious burden given the time constrain to examine each case.

Should applicant traverse on the ground that the pyrazinone and pyridinone species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Susanne Biggs on 5/28/2002 a provisional election was made with traverse to prosecute the invention of Group II, claims 1-10, 13-15, 17-29, 33-38, 41-46 and 49.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 11,12, 16, 30, 31, 32, 39, 40, 47, 48 are withdrawn from further

consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 13-15, 17-29, 33-38, 41-46 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Claim 1 at various places recites the term "about" for example "1 to about 4 carbon atoms" etc., which renders the indefinite. The instant compounds are distinct organic compounds and therefore cannot have less than integer atoms. And as recited it is not clear what is the upper limit of atoms indented. Note

although the term "about" has been held to be acceptable in cases dealing with continuous ranges as normally encountered in process art, in the instant situation, they are imprecise and vague and impart ambiguity to the claim. Deletion of "about" is suggested. See Amgen v Chugai Pharmaceutical Co. 18 USPQ 2d 1016.

2. Recitation of the term "including" in the definition of R_1 group (entry 5) in instant claim 1 renders the claim indefinite as the transitional phrase "including" is open-ended and can include more than what is being positively recited therein. See MPEP 2111.03 which states: The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

3. Claim 1 is also indefinite as it is not clear whether it is a compound claim or a composition claim comprising the compound and a pharmaceutically acceptable salt. Note the last line of the claim 1 recites "and pharmaceutically acceptable salts thereof" which is an improper Markush if the claim is meant to be a compound claim. Replacement of "and" by or" would obviate this rejection.

4. Claim 33 is indefinite as it includes compounds, which are outside the scope of elected subject matter. Note pyrazinone compounds are included in Figure IA and IB.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diseases, does not reasonably provide enablement for prevention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to 'a preventive and/or remedy for thrombosis or embolism' and various diseases related to thrombosis including cerebral infraction, cerebral embolism, myocardial infraction, deep vein thrombosis etc. The scope of the claims includes not only treatment (note remedy is synonymous with treatment) but also "**prevention**" of diseases which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 354-365. The instant compounds are disclosed have FXa inhibitory activity which relates to inhibition of thrombin and it is recited that the instant compounds are useful in 'treating or preventing' several diseases, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and

Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rauch et al., (PubMed Abstract enclosed) wherein with regards to antithrombotic therapies, it is stated that "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al., (PubMed Abstract enclosed) with regards to therapeutic approach of thromboembolic disorders, expresses that 'thrombin inhibitors have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in preventing diseases that require thrombosis inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the pharmacokinetics and anticoagulant effects of thrombin inhibitors are unpredictable.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the 'preventive' effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show preventive effect and the state of the art is that the effects of thrombin inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace not only treatment but also the **prevention** of diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed

compounds towards 'preventing' the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Allowable Subject Matter

Claims 1-31 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action. The closest prior art Sanderson et al. WO 97/01338 teaches several pyridone compounds as thrombin inhibitors useful for treating thrombosis, but differs from instant compounds in having heteroarylalkyl group instead of instant heteroaryl group embraced in E definition. Hence, said claims would be allowed since specific species embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

5/26/2002